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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/325,602	06/03/1999	ALPHONSE GALDES	CIBT-P02-069	3009

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EXAMINER

BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 10/02/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/325,602

Applicant(s)

Galdes

Examiner

Michael Brannock, Ph.D

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-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 2, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above, claim(s) 5-10 and 12-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 21, 4/23/02, have been entered in full.
2. Claims 1-21 are pending. Claims 5-10 and 12-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as set forth in the previous Office Action 15, 10/25/00. Further, Applicant is again reminded that claims 1-4 and 11 will be examined only to the extent that they read on the elected species of a method for promoting the in vitro survival of dopaminergic and/or GABAergic neurons wherein said method comprises the administration of Sonic hedgehog, as elected in Paper #6, 8/23/02.
3. Applicant is notified that any outstanding rejection or objection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and/or persuasive arguments put forth in Paper 19. Further, the Declaration filed on 4/23/02 under 37 CFR 1.131 is sufficient to overcome the Pepinsky et al. reference.

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Maintained Rejections:

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/17924 to Beachey et al., and/or U.S. Patent No: 5789543 to Ingham et al., in view of Muranishi et al., Journal of Controlled Release, 19:179-188, 1992, as set forth previously on page 5 of Paper 17.

In Paper 23, 7/15/02, Applicant argues that the peptide hormones studied by Muranishi et al. had molecular weights that range from about 362 Daltons to about 6000 Daltons, yet the instant sonic hedgehog is 19000 Daltons; thus, Applicant argues that the ordinary artisan would not have been motivated to modify the hedgehog protein, with reasonable expectation of success, because the hedgehog protein is so large. This argument has been fully considered but not deemed persuasive. Muranishi et al. report the successful modification of peptides that differ in molecular weight over a range of almost 10 fold. The hedgehog protein is only about 3 times larger than the tetragastrin peptide. Thus, the skilled artisan would be reasonably confident that the hedgehog protein could be successfully modified as taught by Muranishi et al.

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New Rejections:

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-4 and 11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

The recitation of the term “ hedgehog polypeptide” without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a “hedgehog polypeptide” and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/18856, Ingham et al., 13 July 1995.

Ingham et al., disclose that administration of sonic hedgehog can be used to treat conditions affecting the survival of Dopaminergic neurons in Parkinson's disease and GABAergic neurons as in Huntington's disease (see page 56). Further, Ingham et al., disclose that the sonic hedgehog can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C₁₆ alkyl).

10. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(b) as being unpatentable over Miao et al., J. Neuroscience, August 1, 1997, 17(15)5891-5899.

Miao et al. disclose that sonic hedgehog polypeptides promotes the survival of post-induction midbrain Dopaminergic and GABAergic neurons *in vitro* (see the Abstract), such cell types being well known to be lost in Parkinson's and Huntington's disease, respectively. Further, the sonic hedgehog polypeptides used by Miao et al. were produced using the Baculovirus expression system which was known at the time to produce cholesterol and fatty acid (e.g. myristoyl and palmitoyl) conjugated sonic hedgehog (see Materials and Methods, and references therein).

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Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, as applied to claims above, and in view of Porter JA *et al.*, *Science* 274(255-259)1996. As set forth above, Ingham et al., disclose methods of treating diseases such as Parkinsonism and Huntington's disease characterized by loss of Dopamine and/or GABAergic neurons, comprising the administration of sonic hedgehog polypeptides, however, Ingham et al., do not mention that the hedgehog polypeptide be modified with a lipophilic moiety. As set forth above, Ingham et al., disclose that the hedgehog polypeptides can be obtained from expression in mammalian or baculovirus expression systems (pg 111), both of which would necessarily result in a lipophilic modification of the protein with an aromatic, e.g. cholesterol modification and a fatty acid modification, e.g. palmitic acid (C₁₂ alkyl).

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. Porter JA *et al.* disclose that mammalian hedgehog proteins derived from eukaryotic expression systems are conjugated to a cholesterol moiety, and suggest that this cholesterol modification is

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required for normal development in animals (see the Abstract). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to use cholesterol modified hedgehog protein as taught by Porter JA *et al.* when treating diseases such as Parkinson's Disease or Huntington's disease as taught by Ingham *et al.* The motivation to do so was provided by Porter JA *et al.*, who stated that the lack of cholesterol modification of hedgehog may account for some of the undesirable effects of perturbed cholesterol biosynthesis on animal development (see the discussion).

13. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham *et al.*, 13 July 1995, as applied to the claims above, and in view of WO 96/29342, Jonassen *et al.*, 26 Sep. 1996.

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods. As set forth above, Ingham *et al.*, disclose methods of treating diseases such as Parkinsonism and Huntington's characterized by loss of Dopamine and/or GABAergic neurons, comprising the administration of sonic hedgehog polypeptides, however, Ingham *et al.*, do not mention that the hedgehog polypeptide be modified with an aromatic hydrocarbon moiety, e.g. derivatives such as phenanthrene, anthracene, naphthalene and naphthacene. Jonassen *et al.* teach the lipophilic moieties such as phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for

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example). Further, Jonassen et al. teach that the particular derivative to use is a matter of routine optimization, depending on the particular disease to be treated (page 7). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to modify the sonic hedgehog peptide with phenanthrene or a derivative as suggested by Jonassen et al. when practicing the treatment methods of Ingham et al.. The motivation to do so was provided by Jonassen et al. who teach that lipophilic modification of peptide protracts the action of the modified peptides (see the Abstract).

14. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miao et al., J. Neuroscience, August 1, 1997, 17(15)5891-5899, as applied to the claims above, and in view of WO 96/29342, Jonassen et al., 26 Sep. 1996.

Although the claims, in their current form, do not require that the sonic hedgehog polypeptides be isolated on the basis of a lipophilic moiety, the claims encompass such methods.

As set forth above, Miao et al. disclose that sonic hedgehog polypeptides promotes the survival of post-induction midbrain Dopaminergic and GABAergic neurons *in vitro* (see the Abstract)

However, Miao et al., do not mention that the hedgehog polypeptide be modified with a fatty acid hydrocarbon derivative, e.g. phenanthrene, anthracene, naphthalene or naphthacene.

Jonassen *et al.* teach that lipophilic moieties such as phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for example). Further, Jonassen et al. teach that the particular

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derivative to use is a matter of routine optimization, depending on the particular disease to be treated (page 7). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to modify the sonic hedgehog peptide with phenanthrene or a derivative as suggested by Jonassen et al. when practicing the treatment methods suggested by Miao et al.. The motivation to do so was provided by Jonassen et al. who teach that aromatic hydrocarbon moieties such as phenanthrene derivatives (e.g. page 4) are useful for modifying peptide hormones because such modifications protract the action of the peptides (see the Abstract for example)

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.


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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB



October 1, 2002



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